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Cardiovascular risk profile in patients treated with sirolimus after renal transplantation

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Cardiovascular risk profile in patients treated with sirolimus after renal transplantation. Renal transplant patients are inherently predisposed to cardiovascular disease (CVD) as a result of prolonged exposure to multiple cardiovascular risk factors. Approximately one half of all late graft losses are due to death with a functioning graft, and CVD is the most frequent cause of death with a functioning graft among these patients. Immunosuppressive therapies associated with a reduced burden of risk for CVD would therefore greatly decrease post-transplantation morbidity and mortality. The nephrotoxic effects observed with the use of calcineurin inhibitors (CNIs), such as cyclosporine (CsA), run counter to the goal of renal transplant therapy. Sirolimus, a more recent immunosuppressive agent with a unique mechanism of action, offers an alternative to CsA. Recent data from a 4-year study investigating early CsA withdrawal from a sirolimus-CsA-steroid (SRL-CsA-ST) combination demonstrated significantly better renal function, lower blood pressure, and improved graft survival after CsA withdrawal. During that trial, the increase in serum lipids induced by sirolimus was generally manageable with lipid-lowering therapy. Further investigation is warranted to evaluate the value of CNI-free therapy compared with CNI-based regimens in reducing cardiovascular risk factors and improving patient and graft survival.

Advances in immunosuppressive therapy have contributed to a marked decrease in acute rejection rates following renal transplantation [1]. However, renal transplant patients are more prone to cardiovascular disease (CVD) compared with the general population, and CVD remains the leading cause of death after kidney transplantation. Cumulative records in the United States Renal Data System (USRDS) from more than 68,000 first kidney transplant patients from 1994 to 2000 show that approximately 40% of patients die from CVD [2]. The high prevalence and accumulation of cardiovascular risk factors before and after transplantation contribute to the high incidence of CVD. Foley et al have reported annual mortality rates resulting from CVD in renal transplant patients and in the general population [3]. The 2 populations were matched by age, sex, and the presence of diabetes. Across all age groups, the annual mortality rate was higher in renal transplant recipients than in the general population. The difference in risk was found to be greater during the early years and tended to diminish with age, as the rate of CVD mortality increased in the general population.

Of the established cardiovascular risk factors, hypertension, post-transplantation diabetes, and hyperlipidemia are more frequently associated with immunosuppressive therapy, and are predictors of chronic rejection [4]. Thus, cardiovascular risk management should consider selecting immunosuppressive regimens that reduce the risk from indirect factors, such as renal dysfunction and acute rejection [5, 6]. Agents that mitigate cardiovascular risk while providing improved efficacy outcomes for renal transplant patients would address this need, thereby reducing morbidity and mortality in this population. This paper discusses the emerging profile of sirolimus therapy in relation to efficacy outcomes and cardiovascular risk factors.

PRECLINICAL DATA

Sirolimus, an mTOR inhibitor, is an immunosuppressive agent with a unique mechanism of action [7, 8]. Sirolimus suppresses graft rejection by interfering with cytoplasmic biochemical cascades that transduce signals from the cell membrane to the nucleus. In animal models of organ transplantation, sirolimus exhibited potent antirejection activity and the ability to prolong allograft survival [8, 9]. Preclinical studies also indicated that sirolimus has no deleterious effects on renal function [10, 11]. Shihab et al [11] concluded that the combination of sirolimus and mycophenolate mofetil (MMF) was particularly promising because it suppressed transforming growth factor beta (TGF-β) and had no effect on glomerular filtration.

In addition to the antagonism of immune cytokine-mediated lymphocyte proliferation, sirolimus inhibits growth factor–stimulated smooth muscle cell

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proliferation and migration [12–15]. Sirolimus was shown to reduce neointimal hyperplasia by its inhibitory effect on arterial smooth muscle [16, 17]. Thus, sirolimus demonstrates activity on both lymphoid and nonlymphoid cells [18]. Studies in a model of graft-versus-host disease (GVD) showed that along with preventing the progression of preexisting GVD, treatment with sirolimus resulted in its partial regression [19]. Additionally, despite elevating serum lipids, sirolimus inhibited atherosclerosis in experimental mouse models of atherogenesis [20, 21].

CLINICAL DATA

The success of sirolimus as prophylaxis for acute renal transplant rejection when used concomitantly with existing therapies has been confirmed in clinical studies. Early studies included a phase 2 trial [22], and 2 phase 3 trials that compared a sirolimus/CsA combination with azathioprine [23] or placebo [24]. These trials demonstrated reduced acute rejection rates, but dose-dependent increases in serum lipids and aminotransferases, and decreases in platelet and leukocyte counts were also observed. Importantly, the phase 3 trials demonstrated that sirolimus exacerbated the nephrotoxic effects of CsA.

Direct comparison of sirolimus versus CsA was carried out by 2 early phase 2 studies conducted in Europe [25–27]. Patients received either CsA or sirolimus in combination therapy with corticosteroids and azathioprine or corticosteroids and MMF. Sirolimus did not exhibit the nephrotoxic properties of CsA, and renal function was enhanced after CsA-free, sirolimus-based therapy. Using the 2-year post-transplantation data from these studies, a follow-up analysis was performed to evaluate the cardiovascular risk factors associated with sirolimus and CsA [28]. A higher incidence of hypercholesterolemia and hypertriglyceridemia was observed in the sirolimus group. Fasting serum cholesterol and triglyceride levels peaked at month 2, and declined through month 12, whereafter levels stabilized. The decrease in triglyceride and cholesterol levels in the sirolimus group from month 2 onward coincided with the initiation of protocol-specified lower sirolimus target trough levels, the tapering of steroid doses, and the introduction of lipid-lowering therapy. The 2-year data continued to show favorable outcomes with respect to risk factors, such as hypertension and renal function, in response to sirolimus therapy as compared with CsA therapy. No significant differences were seen between the sirolimus- and CsA-based treatment groups in the incidence of total diabetes and insulin-dependent diabetes and in the frequency of death due to cardiovascular events. Thus, the benefits of decreased hypertension and improved renal function were evident with sirolimus therapy; however, poor lipid profiles were a side effect that had to be managed with increased use of lipid-lowering therapy.

A subsequent study by Flechner et al directly comparing sirolimus with CsA reported improved outcomes by adding an induction agent and reducing the doses of sirolimus to minimize side effects [29]. Their randomized phase 2 trial employed basiliximab as an antilymphocyte induction agent, and sirolimus or CsA in addition to MMF and steroids in primary renal allograft recipients. The results showed comparable outcomes for patient survival, graft survival, and biopsy-confirmed acute rejection, and significantly better renal function in sirolimus-treated patients. Fasting lipid levels, although higher when compared with baseline, were similar in both the sirolimus and CsA groups at all intervals studied in the 1-year period. Thus, a sirolimus-based regimen without CsA was found to confer significant renal function advantages, thereby potentially alleviating the risk of chronic allograft nephropathy.

Recognizing the value of obtaining lower acute rejection rates while reducing the nephrotoxicity associated with the CsA and preserving the sirolimus-related cardiovascular benefits of lower hypertension and improved renal function, a phase 2 study evaluated whether renal function could be further improved by eliminating CsA from a sirolimus-CsA regimen [30]. This study investigated a regimen of full-dose CsA (microemulsion) plus fixed-dose sirolimus (2 mg/day, solution formulation) versus CsA withdrawal plus concentration-controlled sirolimus (trough levels 10 to 20 ng/mL). All patients also received corticosteroids. At 12 months after transplantation, renal function was significantly better in the CsA elimination group. The incidence of hypertension, edema, hypomagnesemia, and dyspnea was also significantly lower in these patients. Comparison of the full-dose CsA group with the CsA-withdrawal group revealed significantly lower serum creatinine levels and significantly higher glomerular filtration rates (GFR) in the latter. The CsA-withdrawal group, however, used higher doses of sirolimus, and was associated with higher rates of abnormal liver function tests, diarrhea, hypokalemia, and thrombocytopenia. Graft and patient survival rates were similar in the 2 groups. Thus, concentration-controlled sirolimus with early withdrawal of CsA resulted in improved renal function without a significant increase in the number of acute rejection episodes.

Nearly concurrent with the above-mentioned phase 2 trial, a phase 3 trial of early CsA withdrawal, the Rapamune Maintenance Regimen (RMR) study, was conducted using the sirolimus tablet formulation [31]. The regimen comprised the administration of sirolimus (2 mg), CsA, and steroids after transplantation, followed by randomization to CsA withdrawal at 3 months with sirolimus trough concentrations targeted to 20 to 30 ng/mL (immunoassay) until month 12, and 15 to

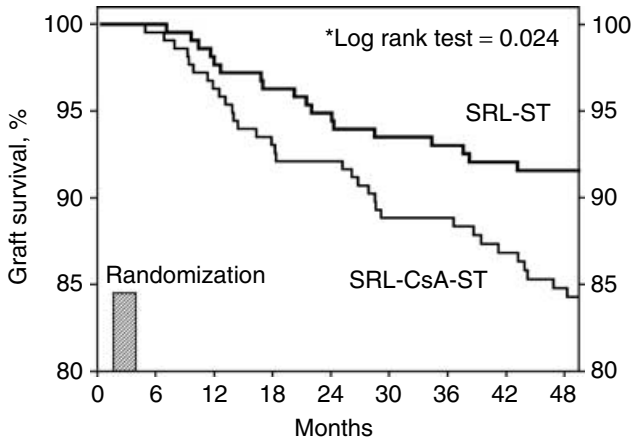

Fig. 1. Graft survival, censored for loss to follow-up, in the Rapamune Maintenance Regimen study.

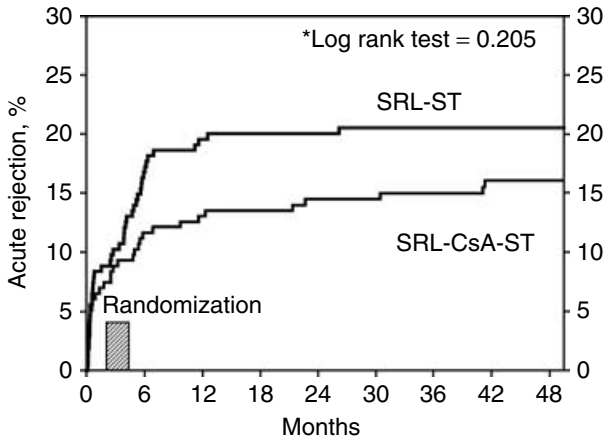

Fig. 2. Incidence of first biopsy-confirmed acute rejection in the Rapamune Maintenance Regimen study.

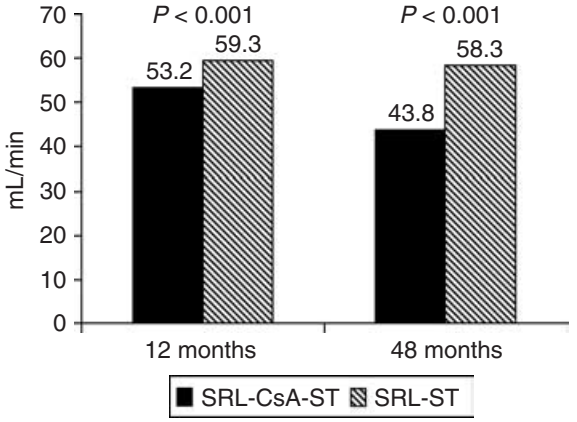

Fig. 3. Calculated glomerular filtration rates (Nankivell method) in the Rapamune Maintenance Regimen study, intention to treat analysis.

25 ng/mL thereafter. The results of this study further confirmed that CsA withdrawal provides benefits of improved renal function and lower blood pressure. At 12 months [31], both groups showed similar patient survival and graft survival rates. Acute rejection rates were 4.2% and 9.8% for SRL-CsA-ST and SRL-ST, respectively ($P = 0.035$). At 24 months [32], no statistically significant differences were seen between the 2 groups with respect to patient survival, graft survival, acute rejection after randomization, and discontinuations. In patients who had CsA withdrawn, serum creatinine levels were significantly better (167 vs. 128 μmol/L, $P < 0.001$), as was the slope of 1/creatinine, and systolic blood pressure was significantly lower (141 vs. 134 mm Hg, $P < 0.001$). High-density lipoprotein (HDL) cholesterol was significantly higher in the SRL-ST group, whereas total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels were not significantly different between the 2 groups. Analysis at 36 months [33] showed a continuing beneficial trend in graft survival in the SRL-ST group. Acute rejection rates from randomization to month 36 were not significantly different from those in the SRL-CsA-ST group; however, serum creatinine levels were significantly better and overall renal function improved or remained stable in SRL-ST group. Lipid parameters were similar between groups, and the cumulative use of statins was comparable.

At 48 months in the RMR study [34], graft survival censored for loss to follow-up was significantly better after CsA withdrawal, either when including death with a functioning graft as an event (84.1% vs. 91.5%, $P = 0.024$, Fig. 1), or when excluding it (90.5% vs. 96.1%, $P = 0.025$). No significant differences were observed in the incidence of death (7.9% vs. 4.7%) or biopsy-proven acute rejection after randomization (7.0% vs. 10.2%, SRL-CsA-ST vs. SRL-ST, respectively). Figure 2 shows the 4-year acute rejection rates based on Kaplan-Meier estimates. As illustrated in Figure 3, calculated GFR, including values from discontinued patients, and setting GFR to 0 for functional graft loss, was significantly higher (43.8 vs. 58.3 mL/min, $P < 0.001$) with CsA withdrawal. Mean arterial blood pressure (101.0 vs. 97.6 mm Hg, $P = 0.046$, Fig. 4) was lower in the SRL-ST group, despite significantly less antihypertensive therapy ($P < 0.001$). Hemoglobin (126.4 vs. 135.6 g/L, $P = 0.031$) was also significantly better in patients treated with SRL-ST. Concerning fasting lipid parameters, the only significant difference between the 2 groups was total cholesterol, which was approximately 0.5 mmol/L higher in the SRL-ST group (Fig. 5). It should be noted that nearly all patients were on lipid-lowering therapy: The cumulative frequency of statin use was 76.7% versus 80.5%, and cumulative fibrate use was 26.5% versus 27.0% in the SRL-CsA-ST versus SRL-ST groups, respectively. The incidence of treatment-emergent diabetes mellitus (both insulin and non–insulin-dependent) was 7.0% in both groups. Thus, the cumulative 4-year data demonstrated superior outcomes for

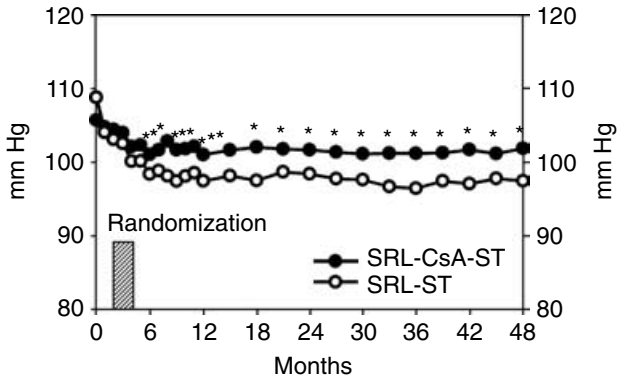

Fig. 4. Mean arterial blood pressure in the Rapamune Maintenance Regimen study, last observation carried forward (LOCF) analysis.

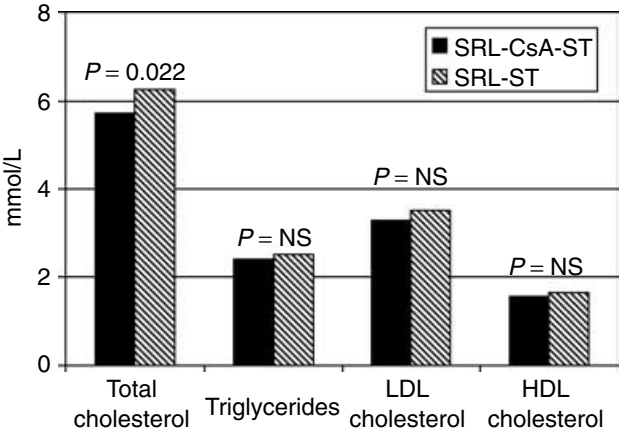

Fig. 5. Serum lipid parameters at 48 months in the Rapamune Maintenance Regimen study.

renal function, stabilized lipid values, and the ongoing benefit of lower blood pressure in patients receiving SRL-ST.

DISCUSSION

The high morbidity and mortality due to CVD in renal transplantation patients emphasizes the need to control cardiovascular risk factors in order to improve patient outcomes. Many of the well-recognized risk factors associated with CVD in the general population are relevant in these patients. The number of acute rejection episodes has been found to be positively correlated with post-transplantation cardiovascular risk [35, 36]. Reduced renal function is associated with increased cardiovascular death in kidney transplantation [37]. Calcineurin inhibitor-based therapies are associated with impaired renal function and an increase in cardiovascular risk factors, although some of these risk factors, such as hyperlipidemia and hypertension, may be less marked with tacrolimus [6, 38]. Continuous treatment with calcineurin inhibitors has long been associated with nephrotoxicity leading to progressive renal dysfunction [39]. Hence, regimens that decrease or eliminate CsA are expected to show decreased nephrotoxicity. Nonetheless, the goal of low acute rejection rates should not be compromised. A regimen including early withdrawal of CsA from sirolimus-CsA-steroid therapy demonstrated at 48 months, that patients who had CsA withdrawn showed numerically higher rates of biopsy-proven acute rejection ($P = 0.205$), but significantly better calculated GFR ($P < 0.001$), mean arterial blood pressure ($P < 0.05$), and graft survival ($P = 0.025$).

Data from several studies indicate that the cardiovascular risks associated with sirolimus appear to be limited to increased plasma lipid levels. Total and LDL cholesterol have been reported to be generally elevated in transplantation populations [40]. A study that assessed the clinical relevance of the effects of sirolimus on plasma lipids by using the Framingham risk model and lipid data from 2 controlled trials concluded that the coronary heart disease risks associated with the cholesterol elevations were small compared with the baseline risks of transplantation patients [41]. It is also relevant to note that a sirolimus-coated stent has been proven to be superior to the traditional bare-metal stent in the prevention of restenosis after coronary angioplasty in humans [42].

CONCLUSION

Sirolimus therapy is non-nephrotoxic and does not produce hypertension or increase the incidence of post-transplantation insulin-dependent diabetes [26]. The hyperlipidemia commonly seen is usually manageable with treatment. Moreover, the observed inhibitory effects of sirolimus on the intimal lining of arteries may have a potentially favorable impact with respect to CVD. Thus, concentration-controlled sirolimus therapy initially combined with short-term CsA therapy offers improved efficacy outcomes along with a reduced incidence of hypertension, ultimately resulting in enhanced graft survival. This emerging profile is encouraging with respect to cardiovascular risk in renal transplant patients. Phase 3 trials are warranted to compare sirolimus-based treatment directly with CsA and tacrolimus therapy, in both de novo and late conversion renal transplantation, to further evaluate the promise of CNI-free therapy in reducing cardiovascular risk factors and improving renal function and graft survival.

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